the two groups. Flow-mediated dilatation (FMD) assessed in isolated-perfused mesenteric arteries was abolished by LPS in flox mice and was improved in endoPTP1B-/- mice. Left ventricular systolic function is altered by LPS injection. In flox mice, LPS induce severe vascular dysfunction shown by the decreased fractional shortening and cardiac index which was improved in endoPTP1B-/- mice. Endo PTP1B-/- mice showed a marked decrease in mortality.

Finally, endothelial PTP1B deletion in mice causes an improvement in cardiovascular function and survival. Additional molecular biological studies will be conducted to understand the mechanisms involved in inflammation, oxidative stress and endoplasmic reticulum stress.

0329

Role of the estrogen receptor alpha (ERalpha) in the vascular response to shear stress in mice

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Small resistance arteries regulate peripheral tissue perfusion following variations in arterial pressure and blood flow. An alteration of the acute flow-mediated dilation (FMD) in response to an elevation in intra-arterial shear stress is the hallmark of early vascular dysfunction and ageing. We recently showed that flow-dependent arterial remodeling, an adaptive phenomenon lost with age, was controlled by the endothelial estrogen receptor alpha (ERα). Our goal was thus to evaluate the role of ERα in endothelial mechano-sensitive mechanisms related to the acute response to flow, by using multiple models of ERα deficiency in male mice, avoiding the hormonal influence of estrogens encountered in females.

The evaluation of the FMD was performed on pressurized mesenteric resistance arteries mounted on an arteriograph following step increase in intraluminal flow (6-100 µl/min). Arteries were isolated from wild-type (WT) and ERα genetically modified male mice deficient in (i) total ERα (ERαKO), (ii) the ligand-dependent transactivation function AF2 (AF2°) or (iii) the plasmic membrane-located ERα following a point mutation of the palmitoylation site of the receptor (C451A).

We first observed a selective alteration of FMD, without any major modification in response to vasodilator agonists (acetylcholine), in male mice deficient in total ERα. Interestingly, while the activation of the AF2 function involved in the nuclear action of ERα seemed only partially involved (% dilation 50µl/min: AF2: 49,5+/-11,8 vs. WT: 68,0+/-7,9 p=ns.), a default in receptor membrane addressing in C451A male mice markedly altered FMD (% dilation 50µl/min: C451A:29,4+/-5,1 vs. WT:59,3+/-10,6 ; p<0,05). We thus show, for the first time, that membrane ERα contributes to arterial shear-sensing and could be pointed out as a new therapeutical target in peripheral vascular diseases, overcoming the known pro-cancerous action of nuclear ERα stimulation.

0042

Chronic increase in blood flow in rat mesenteric resistance arteries improved endothelium (NO)-mediated dilation: essential role of estrogens

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Resistance arteries (RA) have a key role in the control of local blood flow. They undergo outward expansive remodeling in response to a chronic increase in blood flow as seen in post-ischemic collateral arteries growth. This remodeling is associated with improved endothelium-dependent dilation. We hypothesized that estrogens play a role in flow-mediated improvement of endothelium-dependent dilation.

Local increase in blood flow in one mesenteric artery was obtained local surgery in three-month old ovariectomized female rats treated or not with 17-b-estradiol (E2). Changes in arterial function and structure were measured after 2 weeks.

After 2 weeks, arterial diameter increased in high flow (HF) compared to normal flow (NF) arteries in ovariectomized rats treated with E2, not in untreated rats. Acetylcholine-mediated relaxation was higher in HF than in NF arteries in control and OVX rats treated with E2. In untreated rats, the relaxation was lower in HF than in NF vessels. eNOS expression level was higher in HF than in NF vessels in E2-treated rats only. Acetylcholine-mediated relaxation was fully dependent on the production of NO in E2-treated rats (total inhibition by the NO-synthesis blocker L-NAME). In untreated OVX rats L-NAME blocked only partly the relaxation. Endothelium-independent relaxation (sodium nitroprusside) was not affect by OVX or by E2. Serotonin- and phenylephrine-mediated contraction was higher in HF than in NF arteries in both treated and untreated OVX rats.

Thus, we demonstrated the essential role of endogenous E2 in flow-mediated improvement of endothelium (NO)-mediated dilation in mesenteric resistance arteries.

0461

Comparison of cardiovascular responses to nitrogen dioxide and diesel exhausts. An experimental study with controlled exposures to air pollutants

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Traffic air pollution is a major health problem and is recognized as an important risk factor for cardiovascular disease. Even so the role of particles-induced adverse health effects is well established, recent studies outlined the contribution of nitrogen dioxide (NO2) in these effects, in particular on the cardiovascular function. The main sources of this pollutant are oxidation catalysts used to reduce emissions of carbon monoxide and non-methane hydrocarbons from the exhaust of diesel engines and also to facilitate filter regeneration. However, the contribution of NO2 compared to other gaseous and particulate pollutants remains unknown. Consequently, the main objective of this study was to analyze the specific contributions of NO2 in the traffic-related air pollution-induced cardiovascular adverse effects. For this, Wistar rats were exposed for 3 weeks (3h/day, 5 days/week) to either a continuous flow of catalyzed diesel exhaust (DE), particle free or whole DE (particles concentration 2mg/m3), either to a continuous flow of NO2 used at a concentration identical to that measured in the exhaust line. The composition of the emission and the NO2 analyses were monitored on-line during the whole experiment. We evaluated cardiac function and biological effects after 16h recovery in clean air. DE or NO2 exposures induced a modest cardiac dysfunction characterized by an increase in left ventricular diameters and a decrease in fractional shortening. In the case of DE, the presence of particles did not worsen the impairment of cardiac function. In parallel to this effect, mitochondrial function was altered as illustrated by the reduction of the oxygen consumption and of the ATP production. Mitochondrial reactive oxygen species was increased only by the NO2 exposure. In conclusion, these results suggest that DE-induced cardiac dysfunction is due to, at least in part, to NO2 present in DE.

0425

Comparative effect of oxidative stress induced by cigarette and water pipe smoke on the isolated rabbit heart

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Tobacco smoke contains a variety of chemicals including nicotine, irritating, toxic and carcinogenic products… It is the cause of hundreds of thousands of deaths worldwide every year. Water pipe (argyle) has recently become a vogue that has taken an extraordinary extent in several countries. Our study is focused on the oxidative stress of tobacco smoking on the heart through free radicals (FR) produced in water pipe smoke,